REMARKS

Claims 1-8 are all the claims pending in the application.

I. Response to Claim Rejections under 35 U.S.C. § 103

In paragraph 2 of the Office Action, claims 2-7 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Furuya et al (U.S. 6,297,379) as evidenced by Hara et al (The Journal of Clinical Endocrinology & Metabolism, 2003, Vol. 88, No. 4, pp. 1697-1704) and Freedman (American Journal of Human Biology, 2001, Vol. 13, pp. 453-464).

In paragraph 3 of the Office Action, claims 2-5 and 7 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Furuya et al (U.S. 6,048,863) as evidenced by Hara et al (The Journal of Clinical Endocrinology & Metabolism, 2003, Vol. 88, No. 4, pp. 1697-1704) as applied to claim 2 above, and as further evidence by Freedman (American Journal of Human Biology, 2001, Vol. 13, pp. 453-464).

In paragraph 4 of the Office Action, claims 2-4 and 7 are rejected under 35 U.S.C. § 103(a) as beingunpatentable over Furuya et al (U.S. 6,001,850) as evidenced by Hara et al (The Journal of Clinical Endocrinology & Metabolism, 2003, Vol. 88, No. 4, pp. 1697-1704) and Freedman (American Journal of Human Biology, 2001, Vol. 13, pp. 454-464) as applied to claims 2 and 7 above.

In paragraph 5 of the Office Action, claims 2-4 and 7 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Furuya et al (6,187,788) as evidenced by Hara et al (The Journal of Clinical Endocrinology & Metabolism, 2003, Vol. 88, No. 4, pp. 1697-1704) and

Freedman (American Journal of Human Biology, 2001, Vol. 13, pp. 453-464) as applied to claims 2 and 7.

In each rejection, the Examiner's finding of obviousness is partially based on the assertion that each of the four Furuya et al patents teaches treatment or prevention of sex hormone-dependent diseases and hot flashes is a sex-hormone dependent condition.

In response to Applicants' previous arguments presented in the Amendment filed October 12, 2004, the Examiner takes the position that even though sex hormone levels are lowered in patients suffering from hot flashes, the sex hormone is still involved in the condition of hot flashes. According to the Examiner, Freedman (American Journal of Human Biology, 2001, Vol. 13, pp. 453-464) teaches hot flashes most commonly occur with the estrogen withdrawal at menopause (abstract), suggesting that the lowering of estrogen is involved with hot flashes. The Examiner concludes that estrogen is still involved in the hot flash condition and thus hot flashes are considered a sex hormone-dependent condition.

Applicants respectfully traverse the rejection for the reasons of record, which are incorporated herein by reference and additionally in view of the following.

Applicants submit that (1) the cause of hot flashes is not sex hormone-dependent; and (2) the compounds taught by the Furuya et al references are used for treatment of conditions that are caused, exaggerated or maintained by sex hormones, so one of ordinary skill in the art would not have had a reasonable expectation of success of employing the compounds taught by Furuya et al for treating hot flashes which are shown to occur under conditions where sex hormone levels are lowered.

The Examiner asserts that the Abstract of Freedman et al, American Journal of Human Biology, submitted by Applicants teaches hot flashes most commonly occur with estrogen withdrawal at menopause. However, as previously pointed out, Freedman actually states:

> Although hot flashes accompany the withdrawal of estrogen at menopause, *the decline in estrogen levels is not sufficient to explain their occurrence. Elevated sympathetic activation acting through co-adrenergic receptors contributes to the initiation of hot flashes.*

A reference must be considered for all that it teaches or reasonably suggests to those of ordinary skill in the art and, in its proper context, Freedman et al supports Applicants' position that hot flashes are not sex hormone-dependent.

Further, in the paragraph bridging pages 125S to 126S of Freedman, The American Journal of Medicine 2005, Vol. 118 (128), 124S-130S (of record), there is the following description:

> Although hot flashes accompany the withdrawal of estrogen at menopause, the decline in estrogen levels is not sufficient to explain their occurrence. There is no correlation between hot flash occurrence and plasma, urinary or vaginal levels of estrogen, nor are there differences in plasma levels between symptomatic and asymptomatic women.

This description clearly shows that the reduction of sex hormones is not the only cause of hot flashes.

Even further, at page 761, left column, lines 13-20 of the attached copy of Lancet 2008, Vol. 371, 760-770 (Attachment A), there is the following description:

> The mechanisms causing vasomotor symptoms are not fully understood. One theory is that reduced oestrogen concentrations

> cause decreased endorphin concentrations in the hypothalamus, which increases the release of norepinephrine and serotonin; these neurotransmitters lower the set point in the thermoregulatory nucleus, and trigger inappropriate heat loss.

The term "vasomotor symptoms "corresponds to "hot flashes". That is, this description shows that the mechanism causing hot flashes is not fully understood. Therefore, one cannot say that hot flashes are sex-hormone dependent conditions.

Additionally, the compounds taught by the Furuya et al references are used for treatment of conditions that are caused, exaggerated or maintained by sex hormones. Thus, one of ordinary skill in the art would not have had a reasonable expectation of success of employing the compounds taught by Furuya et al for treating hot flashes which are shown to occur under conditions where sex hormone levels are lowered.

It has been well known that hot flashes often occur in menopausal women. Further, at page 248, left column, lines 10-16 of the attached copy of Arch Women's Ment. Health (2007), Vol. 10, 247-257 (Attachment B), there is the following description:

> Estrogen therapy has been shown to relieve VMS, reducing the number of HFs by as much as 95% in menopausal women (Baerug et al. 1998). In addition, many women who experience an abrupt onset of menopause brought on by oophorectomy have more severe symptoms than women who go through a natural, gradual transition (Hendrix 2005).

This description shows that women who cannot secrete sex hormones due to oophorectomy experience severe menopausal states and lowering of estrogen has a relation to menopausal states. The description also shows that the supplementation of estrogen relieves symptoms of hot flashes due to lowering of estrogen. In other words, there is a possibility that

hot flashes caused by the lowering of estrogen and the related symptoms can be relieved by supplementation of estrogen. More specifically, according to publicly known knowledge, **estrogen is supplied to relieve hot flashes.**

On the other hand, according to the present invention, the thienopyridine derivative, which is known to have GnRH antagonizing activity, i.e., sex hormone level lowering-activity thereby causing lowering of sex hormone levels, is useful for treatment of hot flashes.

This is unexpected and not obvious to a person skilled in the art.

As Applicants have previously pointed out, the Furuya et al references teach that the disclosed compounds are useful for preventing and/or treating sex hormone-dependent cancers, prostatic hypertrophy, hysteromyoma, endometriosis, precocious puberty, amenorrhea, premenstrual syndrome, multiocular ovary syndrome and acne, which are conditions that are caused, exaggerated or maintained by sex hormones. In other words, the conditions taught by the Furuya et al references are conditions where sex hormones are increased.

To the contrary, as stated above, hot flashes occur under conditions where sex hormone levels are lowered, which is the opposite effect from the conditions taught by Furuya et al.

Thus, one of ordinary skill in the art would not have had a reasonable expectation of success of treating a condition which occurs where sex hormone levels are lowered by administering an agent shown to be effective in conditions which are caused, exaggerated or maintained by sex hormones. Accordingly, it would have been expected that there would be a possibility that the thienopyridine derivative of the present invention causes hot flashes because such a derivative is known to have GnRH antagonizing activity, i.e., sex hormone level lowering-activity.

Further, Hara et al does not remedy the deficiencies of Furuya et al since Hara et al relates to hormone-dependent diseases such as endometriosis, uterine leiomyomas and breast cancer (page 1701, 2nd column) and does not specifically relate to hot flashes. Freedman et al also fails to remedy the deficiencies of Furuya et al.

In view of the above, Applicants submit that one of ordinary skill in the art would not have had a reasonable expectation of success of achieving the presently claimed method of treating hot flashes based on the teachings of Furuya et al, Freedman et al and/or Hara et al.

Accordingly, Applicants respectfully request withdrawal of the §103 rejections.

II. Response to Obviousness-Type Double Patenting Rejections

In paragraph 7 of the Office Action, claims 4 and 7 are rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claim 13 of Furuya et al (U.S. 6,001,850) as evidenced by Freedman (American Journal of Human Biology, 2001, Vol. 13, pp. 453-464).

In paragraph 8 of the Office Action, claims 4 and 7 are rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claim 8 of Furuya et al (U.S. 6,048,863) as evidenced by Freedman (American Journal of Human Biology, 2001, Vol. 13, pp. 453-464).

In paragraph 9 of the Office Action, claims 4 and 7 are rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claim 4 of Furuya et al (U.S. 6,187,788) as evidenced by Freedman (American Journal of Human Biology, 2001, Vol. 13, pp. 453-464).

In response to the rejections, Applicants submit that the arguments above with respect to the Furuya et al references and Freedman traversing the obviousness rejections apply to these obviousness-type double patenting rejections as well, and thus withdrawal of the rejections is respectfully requested.

III. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

Jennifer M. Hayes
Reg. No. 40,641

for Michael R. Dzwonczyk
Registration No. 36,787

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860
WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: June 11, 2008

Menopause

Heidi D Nelson

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Oregon Evidence-based Practice Center, Department of Medical Informatics and Clinical Epidemiology and Department of Medicine, Oregon Health and Science University, OR, USA; and the Women and Children's Health Research Center, Providence Health and Services, Portland, OR, USA (H D Nelson MD)

Correspondence to: Dr Heidi D Nelson, Oregon Health and Science University, Mailcode BICC, 3181 SW Sam Jackson Park Road, Portland, OR 97239, USA
nelsonh@ohsu.edu

Menopause is the time of life when menstrual cycles cease, and is caused by reduced secretion of the ovarian hormones oestrogen and progesterone. Although menopause is a normal event for women, individual experiences vary, and some women seek medical advice for the management of symptoms. Many symptoms have been attributed to menopause, but only vasomotor dysfunction and vaginal dryness are consistently associated with this time of life in epidemiological studies. Other common symptoms such as mood changes, sleep disturbances, urinary incontinence, cognitive changes, somatic complaints, sexual dysfunction, and reduced quality of life may be secondary to other symptoms, or related to other causes. Trials of therapies for vasomotor dysfunction have shown improvements with oestrogen, gabapentin, paroxetine, and clonidine, but little or no benefit with other agents; adverse effects of these treatments must also be considered. Many questions about menopausal transition and its effects on health have not been adequately addressed.

Introduction

The transition to menopause is a complex physiological process, often accompanied by the additional effects of ageing and social adjustment. Historically, much medical knowledge of menopause drew on convention rather than on rigorously designed studies, which led to inappropriate care. Moreover, at times serious symptoms were regarded as normal concomitants of the time of life and not addressed further, and mild symptoms were overmedicalised.

Menopause results from reduced secretion of the ovarian hormones oestrogen and progesterone, which takes place as the finite store of ovarian follicles is depleted. Natural menopause is diagnosed after 12 months of amenorrhoea not associated with a pathological cause. Menopause can also be induced by surgery, chemotherapy, or radiation. Initially, the menstrual cycle lengths become irregular, and follicle-stimulating hormone (FSH) concentrations rise in response to decreased concentrations of ovarian hormones. As the menopausal transition progresses, menstrual cycles are missed and ultimately stop, as does ovulation. For some women, 3 consecutive months of amenorrhoea, or mean cycle lengths longer than 42 days, are predictors of impending menopause.[2,3]

Several terms have been used to describe the events that take place during the menopausal transition. A model developed at the Stages of Reproductive Aging Workshop (STRAW)[4] described seven stages of reproductive ageing (figure 1), which were subdivided into reproductive stages, characterised by regular menstrual cycles; menopausal transition stages, with variable menstrual cycles and high FSH values; and postmenopause stages, beginning with the final menstrual period, and lasting until the end of life. Definitions and models continue to be assessed and refined for clinical and research applications.[5–7] Although models are useful to describe the general progression of events leading to menopause, substantial individual variation exists, including skipping stages and moving back and forth between stages.[8]

The menopausal transition usually begins when women are in their mid-to-late 40s, and can last several years, most commonly 4–5 years.[9] The final menstrual period generally happens when women are between 40 and 58 years old,[9] and a final menstrual period before 40 years of age is regarded as premature. Population studies suggest that smoking and low socioeconomic status are associated with premature final menstrual periods.[10] Other factors can affect the age at which women have their final menstrual period, including age at menarche, parity, previous oral contraceptive use, body-mass index, ethnic origin, and family history.[11] The age at which women have their final menstrual period varies across large surveys done in different countries. Mean ages of 50–51 years were reported in Italy, Iran, Slovenia,[11] and the USA;[12] and of 47–50 years in Korea, Lebanon, Singapore, Greece, Morocco, Mexico, Taiwan, and Turkey.[11]

Search strategy and selection criteria

Relevant studies were identified from comprehensive searches of MedLine (1966 to December, 2006) and the Cochrane database of systematic reviews and controlled trials (last accessed December, 2006). Search strategies focused on menopausal symptoms and therapies for symptoms using the terms climacteric and menopause with terms depression, depressive disorder, affect, mood disorders, quality of life, sex disorders, dysfunction, sleep disorder, urination disorder, vasomotor symptom, somatic symptom, and vaginal dryness, and with specific terms for treatments such as estrogen, androgen, progestin, tibolone, antidepressants, gabapentin, etc. Specific searches are described in a previous publication[1] and were updated for this Seminar. Additional articles were obtained by searching recent systematic reviews, reference lists of related articles, and websites, and by consulting experts. Non-English studies were included if they were sufficiently described in English-language abstracts. For symptoms, prospective cohort studies of the menopause, examining at least one potential menopausal symptom, were included; cross-sectional studies with similar criteria were examined for contributory data, such as prevalence rates of symptoms. For therapies, randomised, double-blind, placebo-controlled trials, providing data on the treatment of menopausal symptoms with one or more therapies, were included, as were meta-analyses of relevant trials. Trials without a placebo group, comparing therapies, were excluded, because of difficulty in interpreting their results. Studies were included whether the women were recruited from health-care settings, or the general population.

Clinical manifestations

Many clinical manifestations have been attributed to menopause. Vasomotor episodes manifest as spontaneous sensations of warmth, usually felt on the chest,

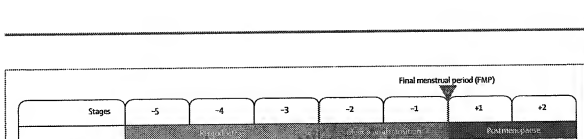

Figure 1: Stages of normal reproductive ageing in women
Reproduced with permission from Soules and colleagues.[4] FSH=follicle-stimulating hormone.

neck and face, and often associated with perspiration, palpitations, and anxiety. These episodes are described as hot flushes, hot flashes, and night sweats. The term "hot flush" indicates the sensation of heat; "hot flash" describes episodes with sweating, sometimes followed by a chill; however, the terms are often used interchangeably. Vasomotor episodes are variable in frequency, duration, and severity, are sometimes recurrent, and usually last less than 5 min. They can be triggered by warm environments, hot food or drinks, and stress. For some women, these episodes interfere with activities or sleep to such a degree that medical advice is needed. The mechanisms causing vasomotor symptoms are not fully understood. One theory is that reduced oestrogen concentrations cause decreased endorphin concentrations in the hypothalamus, which increases the release of norepinephrine and serotonin; these neurotransmitters lower the set point in the thermoregulatory nucleus, and trigger inappropriate heat loss.[13–15]

Urogenital problems, such as vaginal dryness, itching, and dyspareunia, are caused by physiological responses to low concentrations of oestrogen and androgens. These responses include reduced vaginal blood flow and secretions, tissue changes, and a change in the pH of vaginal fluid, from acidic to neutral. Additional symptoms, such as anxiety, depression, and mood changes, urinary incontinence and leakage, sleep disturbances, cognitive changes, somatic complaints, and sexual dysfunction have been associated with the menopausal transition. Some of these symptoms are secondary to vasomotor and urogenital symptoms, and others are related to other causes. Factor analysis studies showed that menopausal status is more consistently associated with vasomotor than with psychological or physical symptoms, arguing against a universal menopausal syndrome that includes all of them.[16]

Distinction between clinical signs related specifically to the menopausal transition, and those related to ageing in general, is difficult. Studies of menopausal dysfunctions need to be carefully interpreted, because of methodological inconsistencies and limitations. Many methods have been developed to assess menopausal symptoms, but only a few are standardised, valid, and reliable. Some methods are based on self-reports of the presence, severity, and frequency of individual symptoms, such as hot flashes. Others use cumulative scores, based on lists or scales of symptoms that are thought to be associated with the menopause, such as changes of mood, cognition, quality of life, sexual function, and somatic symptoms. The Green climacteric scale,[17] Kupperman index,[18] and menopause-specific quality of life questionnaire[19] are examples of commonly used scores of menopausal symptoms. The multitude of symptoms studied and methods used often does not allow comparisons between studies, and the populations they represent. Most studies fail to adjust or stratify for potentially important variables such as age,

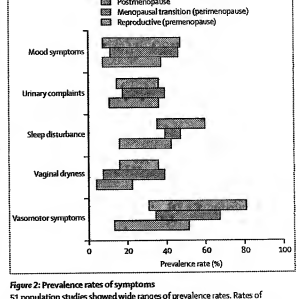

Figure 2: Prevalence rates of symptoms
51 population studies showed wide ranges of prevalence rates. Rates of vasomotor symptoms, vaginal dryness, and sleep disturbances are higher for women in menopausal transition and postmenopause than for women in reproductive stages.

pre-existing disorders, and the use of hormone therapy.

In epidemiological studies, the reproductive stages are often defined by terms that predate the STRAW model.[4] In general, premenopause corresponds to the STRAW reproductive stages; perimenopause corresponds to the STRAW menopausal transition stages; and postmenopause begins at the time of the final menstrual period. However, studies vary in: how these terms are used; the data used to assess menopausal status;[4] which stages are compared; and when and how frequently symptoms are measured. Most studies, including those from prospective cohorts, report cross-sectional data and compare results for premenopausal, perimenopausal, and postmenopausal groups of women, whereas others provide serial measures from individuals as they progress through stages.

Prevalence rates of symptoms, such as vasomotor dysfunctions, vaginal dryness, sleep disturbance, urinary complaints, and mood changes, vary greatly (figure 2).[1] Differences between studies might result from inconsistencies in methods, or from true differences between populations.

Cohort studies have shown that only a few clinical manifestations are significantly associated with the menopausal transition (table 1). Vasomotor dysfunctions, including hot flashes (odds ratio [OR] 1·3–13) and night sweats (OR 2·4–4·3), substantially increase in frequency and severity during the menopausal transition;[20–22] these symptoms are experienced by more than 50% of menopausal women.[1] Although most symptoms resolve within a few months for many women, they can persist for several years after the final menstrual period. About 29% of 60-year-old women report persistent hot flashes.[23] Studies of factors that might affect vasomotor dysfunction are inconclusive, but suggest that body-mass index, exercise, age of onset of menopausal transition, surgical menopause, smoking, and depression might all be implicated.[1]

Vaginal dryness is also associated with the menopausal transition[22] and is reported by up to a third of menopausal women.[1] Additionally, menopausal women have more sleep disturbances than non-menopausal women (OR 1·3–1·5),[20,22] sometimes because of vasomotor symptoms.[22] About 40–60% of women have sleep disturbances during menopause and postmenopause stages.

Several symptoms are inconsistently associated with menopause. Some studies have reported no correlation

	Description (length of follow-up in studies)	Transition from premenopause to perimenopause	Perimenopause stage	Transition from perimenopause to postmenopause	Postmenopause stage
Australian Longitudinal Study on Women's Health	8236 women (45–50 years of age) enrolled in 1996 in Australia (2 years)	Increased hot flashes, night sweats, sleeping disturbances, severe tiredness, and stiff painful joints. No associations with back pain, body pain, headache, urinary leakage, general health perception, general mental health, quality of life, or constipation	Increased hot flashes, night sweats, sleeping disturbances, severe tiredness, stiff painful joints, back pain, body pain, urinary leakage, worse general health perception, and quality of life. No associations with general mental health, headache, or constipation	Increased night sweats and sleeping disturbances. No associations with hot flashes, somatic symptoms (severe tiredness, stiff painful joints, back pain, body pain, headache), urinary leakage, general health perception, general mental health, quality of life, or constipation	Increased night sweats, decreased general mental health. No associations with hot flashes, difficulty sleeping, somatic symptoms (severe tiredness, stiff painful joints, back pain, body pain, headache), urinary leakage, general health perception, quality of life, or constipation
Eindhoven	2103 women born between 1941 and 1947 recruited on the basis of responses to an osteoporosis screening study in Eindhoven, Netherlands (5 years)	No association with depression	No association with depression	Increased depression based on EDS score	
Gothenburg	809 women (38–60 years of age) randomly selected in 1968–1969 and followed up for more than 25 years in Gothenburg, Sweden (6 years)	No associations with development of mental disorder			
Manitoba Project on Women and Their Health in the Middle Years	469 women (40–59 years of age) from Manitoba, Canada (3 years)	No associations with depression (based on CES-D score 16 and over)			
Massachusetts Women's Health Study	241 premenopausal women (45–55 years of age) from Massachusetts, USA (6 years)	No associations with depression (based on CES-D score 16 and over)			
Medical Research Council (MRC) National Survey for Health and Development	1572 women identified from a socially stratified sample of all births in March 1943 in Britain (52 years)	No associations with vasomotor symptoms, anxiety, or depression	Increased vasomotor symptoms; no associations with anxiety or depression	No associations with vasomotor symptoms, anxiety, or depression	

(Continues on next page)

	Description (length of follow-up in studies)	Transition from premenopause to perimenopause	Perimenopause stage	Transition from perimenopause to postmenopause	Postmenopause stage
(Continued from previous page)					
Melbourne Women's Midlife Health Project	494 women (45–55 years of age) from Melbourne, Australia enrolled in 1991 (4–5 years)		Increased sleeping disturbances, decreased quality of life. No association with hot flushes, vaginal dryness, mood, somatic symptoms, urinary symptoms, incontinence, or sexual dysfunction (early perimenopause). Increased hot flushes and night sweats, vaginal dryness, sleeping disturbances, sexual dysfunction, and general wellbeing, decreased breast soreness, and quality of life. No association with mood changes, somatic symptoms, bulkier symptoms, or incontinence (late perimenopause)		Increased hot flushes and night sweats, vaginal dryness, sleeping disturbances, and general wellbeing, decreased breast soreness, and quality of life. No association with mood changes, somatic symptoms, urinary symptoms, or incontinence
National Health Examination Follow-up Study	3049 women (40–60 years of age) from the US National Health and Nutrition Examination Survey (NHANES) (10 years)	No associations with depression or quality of life			
Ohio Midlife Women's Study	208 women (40–60 years of age) from a community in Ohio, USA, including 57% white and 43% African-American women (2 years)	No association with anxiety or depression			
Pennsylvania Ovarian Aging Study	436 women (35–47 years of age) from Pennsylvania, USA, including 50% white and 50% African-American women (4 years)	Increased depression (CES-D score 16 or higher) (transition from premenopause to early and late perimenopause)		No increase in depression score	
Seattle Midlife Women's Health Study	11 222 premenopausal and perimenopausal women (35–55 years of age) from Seattle, USA, census tracts, including different ethnic groups (2–3 years)	No associations with vasomotor symptoms, insomnia, dysphoric or depressed mood, or neuromuscular or somatic symptoms			
Study of Women's Health Across the Nation (SWAN)	3306 women (40–55 years of age), from different community sites in the USA, followed up since 1995 (6 years)	Increased vasomotor symptoms	Increased depressive symptoms (based on CES-D score 16 or higher)		Increased depressive symptoms (based on CES-D score 16 or higher)

EHS=Edinburgh Depression Scale. CES-D=Center for Epidemiologic Studies Depression Scale. PRIME-MD=primary care evaluation of mental disorders. *Summarised from reference 1.

Table 1: Associations of symptoms with menopausal stages* reported in cohort studies

between menopausal transition and mood changes, development of mental disorders, or general mental health;[11,24–26] others—including the Pennsylvania Ovarian Aging Study,[27] the Study of Women's Health Across the Nation (SWAN),[28] and the Eindhoven Perimenopausal Osteoporosis study[29]—have shown associations. The inconsistent results probably indicate methodological differences, especially in how symptoms are measured.[28] No associations have been reported between cognitive change and menopause, in the few studies that have been done;[1] increased somatic symptoms are sometimes reported.[1]

Urinary complaints, including incontinence and leakage, were related to menopause in some,[30] but not all,[22,31] investigations. Women reported decreased sexual responsivity, libido, and frequency of sexual activity with menopause;[16,32] depression and vaginal dryness were reliable predictors of low sexual desire. Although decreased oestradiol concentrations were associated with low sexual function in an Australian cohort, previous sexual and partner issues have more substantial effects than hormonal factors.[16] Studies of quality of life during menopause are conflicting: some have indicated decline, others an improvement, and others no association.[1]

Large cohorts provide useful information about the menopausal transition. However, individual experience can be affected by many additional factors; ethnic origin and culture are important, but whether biological or sociocultural factors have the biggest effect is unclear. Genetics, dietary practices, parity, body-mass index,

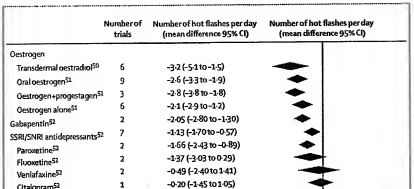

Figure 3: Results of trials of therapies for hot flashes
Hot flashes were reduced by two to three flashes per day with oestrogen, two with gabapentin, about one with paroxetine, and one with clonidine in double-blind, randomised, placebo-controlled trials. Isoflavones had slight or no effect.

physical activity, and environmental exposures differ with ethnic origin and culture, and are likely to affect the menopausal transition as they do other phases of reproductive life,[11] and health in general. Additionally, the perception and description of symptoms vary with cultural context and language. Some women might interpret a vasomotor symptom as a warm sensation, whereas others might describe dizziness or other sensation because it is more culturally meaningful to them.[42]

In SWAN,[36] done in the USA, African-American women reported more frequent vasomotor dysfunctions than did white women, who in turn reported more than did Hispanic, Chinese, and Japanese women.[44,45] White and Hispanic women had sleep difficulties more often than did African-American, Chinese, and Japanese women.[46] Hispanic women reported body pain more frequently than did white women.[47] In surveys done in Asia, most Asian women had body or joint pain rather than vasomotor symptoms, although proportions varied with ethnic group.[48]

Management and treatment

Many questions about the menopausal transition and its effects on health have not yet been adequately answered. Considerable differences exist between individuals from different countries. Even in homogeneous populations, individual experiences of menopause vary, as do experiences of pregnancy. The best possible approach to the management of menopausal symptoms is to address each woman's unique needs.

Surveys in the USA indicate that physicians underestimate their patients' concerns about menopausal symptoms.[49] A correct diagnosis of clinical manifestations and their association with menopause is crucial. Symptoms should be assessed and treated individually and specifically. If treatments for menopausal symptoms are prescribed, understanding their effectiveness and safety is essential.

Many investigators have reported on the treatment of symptoms associated with the menopausal transition. Most randomised, placebo-controlled trials focus on the treatment of vasomotor symptoms. These trials provide useful information for the management of highly symptomatic women, although not all proposed therapies have been sufficiently assessed. Effectiveness varies between therapies; evidence of substantial clinical benefit exists only for a few (figure 3).

Hormones

Oestrogen has been used for many years as a hormonal supplement to treat menopausal symptoms, and is the most effective treatment for vasomotor dysfunction in most women. This hormone is no longer recommended for prevention of chronic conditions,[19] although it is effective and approved for osteoporosis prevention.[1] Oestrogen is provided in several formulations, and is most commonly given by oral, transdermal, or vaginal routes. Women with an intact uterus are prescribed the "combined" or "opposed" regimen, in which oestrogen is combined with progestagen: this is intended to avoid the development of endometrial hyperplasia and endometrial cancer. The combined regimen can be administered on a cyclical basis, in which components are provided on specific days of the month, or on a continuous schedule, in which women take both hormones daily. Women without a uterus can take a daily dose of oestrogen without progestagen (the "unopposed" regimen). Doses vary by formulation, but present recommendations suggest the use of the lowest possible dose, for the shortest duration needed to relieve symptoms.[1] Periodic attempts to taper and discontinue oestrogen treatment are encouraged, to reduce to a minimum potential adverse events, although the best method of discontinuing oestrogen is not known. The interruption of oestrogen therapy can be difficult for many women, who experience a recurrence of symptoms.[34]

The use of oestrogen to treat hot flashes has been studied in many randomised controlled trials; the results are summarised in recent systematic reviews and meta-analyses.[20,51,53,54] Most trials were done in the USA or western Europe, and assessed forms of oestrogen that are common in these countries, especially oestradiol and conjugated equine oestrogen. Trials often recruited participants from primary care or gynaecology practices, focusing on healthy menopausal women in their early 50s; the baseline symptoms varied from study to study.

A Cochrane meta-analysis of randomised controlled trials found that symptomatic women treated with various forms of oral oestrogen had 2·6 fewer hot flashes

	Dose (mg/day)	Number of trials	Number of trials including women with breast cancer	Difference in number of daily hot flashes (95% CI)	Difference in severity or composite score (%)*	Potential adverse effects (selected)†
Gabapentin[57,58]	300–900 mg three times a day	3	1	−2·05 (−2·80 to −1·30); two trials‡	Improved 17–30%	Somnolence, fatigue, nausea, vomiting, and dizziness
SSRI/SNRI						
Paroxetine[59,60]	10–20 and 12·5–25 controlled release	2	2	−1·66 (−2·43 to −0·89); two trials‡	Improved 25–35%	Headache, nausea, drowsiness, and insomnia
Fluoxetine[61]	20–30	2	1	−1·37 (−3·03 to 0·29); two trials‡	Improved 25%	Nausea and dry mouth
Citalopram[61]	20–30	1	None	−0·20 (−1·45 to 1·05)	Improved	Nausea and dry mouth
Sertraline[59,62]	50–100	3	1	Reduced by <1 per day in 2 trials	Improved in 2 trials	Headache, nausea, drowsiness, dry mouth, and dizziness
Venlafaxine[63,64]	37·5–150 extended release	3	1	−0·49 (−2·40 to 1·41); 2 trials‡	Improved 10–35%	Dry mouth, nausea, decreased appetite, constipation, and insomnia
Veralipride[65]	100	3	None	Not reported§	Improved 45% in 2 trials	Mastodynia and galactorrhea
Moclobemide[59]	150–300	1	None	Not reported§	Not reported§	Somnolence
Alkaloids						
Clonidine[66]	Oral 0·025–0·075 mg twice a day; transdermal 0·1	10	2	−0·95 (−3·44 to +0·67); 4 trials at 4 weeks‡ −1·63 (−2·76, to −0·05); 2 trials at 8 weeks‡	Improved 13–26% in 4 of seven trials	Dry mouth, nausea, constipation, insomnia, drowsiness, skin irritation with transdermal form
Methyldopa[67]	375–1125	3	None	No difference	Improved in 1 of 2 trials‖	Dry mouth, nausea, and fatigue
Bellergal Retard[68]	One tablet twice a day (0·6 mg ergotamine, 40 mg phenobarbital, 0·2 mg levorotatory alkaloids)	1	None	No difference	No difference	Dry mouth, dizziness, and sleepiness

SSRI/SNRI=selective serotonin reuptake inhibitor/selective noradrenergic reuptake inhibitor. *Frequency and severity. †Additional adverse effects are described in other sources. ‡Random-treatment-assigned trials. §Between-group differences not reported. ‖Data presented in graphs.

Table 2: Efficacy of non-hormonal prescribed therapies in placebo-controlled trials

per day (95% CI 1·9–3·3) than did women given placebo.[51] This effect was equivalent to a 75% reduction in frequency (0·64–0·82).[51] Oestrogen users also had significantly reduced hot-flash severity, compared with placebo users. The decrease in frequency of hot flashes was similar in women treated with opposed and unopposed oestrogen regimens, than in those treated with placebo, although severity decreased slightly more in women treated with the opposed regimen.

In a systematic review, hot-flash frequency, severity, or both, improved with oral and transdermal forms of oestradiol more than it did with placebo.[50] Oral oestradiol reduced hot flashes by 2·4 per day (1·5–3·2), and transdermal oestradiol by 3·2 per day (1·5–5·1); and results were similar for opposed and unopposed regimens.[50] Trials of oral conjugated equine oestrogen reported similar improvements in hot-flash frequency, severity, or both. Trials comparing oestrogen agents head-to-head (conjugated equine oestrogen *vs* oral or transdermal oestradiol) showed reduced number and severity of hot flashes for all treatment groups, with no substantial differences between them.[50]

Adverse effects of oestrogen have been well studied. Breast tenderness and uterine bleeding are the most common side-effects from short-duration treatment trials.[59] Others include nausea and vomiting, headache, weight change, dizziness, venous thromboembolic events, cardiovascular events, rash and pruritus, cholecystitis, and liver disorders.[59] Oestrogen users have increased breast density, leading to higher rates of biopsy of lesions detected by mammography.[59] Results of the Women's Health Initiative (WHI), a large trial of conjugated equine oestrogen alone or combined with medroxyprogesterone acetate versus placebo, reported increased risks of stroke and venous thromboembolic events with both regimens.[58,59] Risks of coronary heart disease and invasive breast cancer were also higher for those treated with conjugated equine oestrogen and medroxyprogesterone acetate than for those treated with placebo,[58] but not for those treated with conjugated equine oestrogen alone.[59] Secondary analysis of WHI data suggested that women starting hormone therapy within 10 years from the onset of menopause had a reduced risk of coronary heart disease, compared with those who started later.[60] Oestrogen should not be prescribed to women with cardiovascular disease, a history of thromboembolic events, breast or uterine cancer, or liver disease. The effects of other forms of oestrogen, including customised and bioidentical formulations, have not been well studied and are not known.

Few trials of progestagen or progesterone have described their effectiveness as single agents for the treatment of hot flashes; these trials have conflicting[61,62] or inconclusive results.[63–65] In a trial of women with breast cancer, the use of megestrol reduced hot flashes

by 73% compared with 26% with placebo ($p<0.001$).[66] Few trials have reported comparisons of testosterone and oestrogen combinations versus oestrogen alone or placebo. One trial showed no differences between treatment with testosterone and oestrogen versus treatment with oestrogen alone for hot-flash severity.[67] Tibolone is a synthetic steroid with progestogenic, androgenic, and oestrogenic effects. Some trials comparing the effect of tibolone with that of placebo showed decreased severity of hot flashes[68,69] and a decreased score on Kupperman's scale;[70] other trials did not.[1] Common adverse effects of tibolone include uterine bleeding, body pain, weight gain, and headache.[1]

Non-hormonal agents

Concerns about the adverse effects of oestrogen, after the results of the WHI trial were published in 2002,[58] have led to increased interest in non-hormonal therapies for menopausal symptoms. These agents have not been approved by drug-regulating agencies for menopause; moreover, they are associated with adverse effects that are well described (see US Food and Drug Administration). Several trials of non-hormonal therapies enrolled women with vasomotor symptoms who have breast cancer, for whom oestrogen is contraindicated. Whether women with breast cancer have responses to these agents that are different from those of women without cancer is not clear, because of the small number of trials. Trials that compare tamoxifen users and non-users showed similar results;[71] however, whether vasomotor symptoms of women with breast cancer are induced mainly by menopause or by use of tamoxifen is not known.

Use of gabapentin, a γ-aminobutyric acid analogue for treatment of seizures, reduced hot-flash frequency[72,73] and severity[72-74] compared with placebo in three trials (table 2). This reduction is equivalent to about two fewer hot flashes per day.[52] Women reported improvement when treated with 900 mg per day gabapentin,[73,74] but not with 300 mg per day.[73]

Two trials of paroxetine,[75,76] a selective serotonin reuptake inhibitor (SSRI), and two of venlafaxine,[77,80] a serotonin norepinephrine reuptake inhibitor (SNRI), showed a reduction in hot-flash frequency of at least one hot flash per day (table 2).[52] This effect was not significant in other trials of SSRIs and SNRIs. Although some trials of sertraline suggest potential benefits in reducing hot flashes,[77,78] others do not.[82] It has been postulated that hot flashes are linked to an overloading of serotonin-receptor sites in the hypothalamus, which are then blocked by SSRIs or SNRIs.[75] In treatment trials, hot flashes improved earlier than did psychiatric symptoms, and irrespective of coexisting depression and anxiety.[76] For some women, treatment of underlying depression might improve their ability to cope with their hot flashes. Trials of other antidepressants, venlafaxine and moclobemide, have been inconclusive because of methodological limitations.[52]

50% of trials of clonidine, a centrally active antihypertensive α-adrenergic agonist, showed substantially reduced hot-flash frequency or severity, and the other 50% did not.[52] In combination, results from all trials suggest a reduction of about one hot flash per day (table 2).[52] Clonidine might relieve hot flashes by decreasing peripheral vascular reactivity. Trials comparing methyldopa, an α-adrenergic antihypertensive agonist, with placebo showed no significant differences in hot-flash frequency.[52]

Non-prescribed therapies

Trials of non-prescribed therapies are often difficult to interpret because of variability of components and doses. Adverse effects, especially long-term effects, are not as well known as those of prescribed medications. Clinicians should access reliable sources to assess potential benefits and harms of individual agents (for an example, see US National Institutes of Health Office of Dietary Supplements).

Phyto-oestrogens are plant-based substances that bind to oestrogen receptors, and have weak oestrogenic and anti-oestrogenic activities. Soy isoflavone extracts, containing predominantly daidzein, genistein, and their glucoconjugates, show mixed effects on hot flashes in placebo-controlled trials (table 3).[52] In combination, results indicated about one hot flash less per day compared with placebo, although some estimates were not significant.[52] Other systematic reviews drew similar conclusions.[123-125] Few trials of dietary forms of soy—including soy in beverages, powder, flour, protein, cereal, and muffins—reported improvements in frequency or other hot-flash measures (table 3).[1,83,84]

Red-clover isoflavones, containing genistein, daidzein, formononetin, and biochanin, did not improve frequency or severity of hot flashes in placebo-controlled trials (table 3).[52,85,126-131] Similarly, phyto-oestrogens from hop extract,[85] flax,[84,87] and in topical forms,[88,89] did not show benefit in the treatment of hot flashes.

Black cohosh is a herbal therapy (*Cimicifuga racemosa*) believed to have oestrogenic properties. Black cohosh does not reduce the frequency of hot flashes, and although some trials showed improvement of other hot-flash measures,[90-92] others did not[93-96] (table 3). Results are also ambiguous when black cohosh is added to soy isoflavones[97,98] or St John's wort.[99] Black cohosh has been associated with liver damage.[122]

Several trials assessing Chinese herbs showed no differences in hot flashes compared with placebo.[1,83] Single trials of other supplements, such as evening primrose oil,[100] phospholipid liposomes,[101] and pollen extract[102] reported some improvements in hot-flash measures, but most did not (table 3).[103-107] One small trial of osteopathic manipulations reported improved hot flashes and night sweats.[108] Trials of reflexology,[109] magnets,[110] and aerobic exercise[111] showed no improvement in hot-flash measures compared with

	Types and doses (mg/day)	Number of trials (including women with breast cancer)	Difference in number of daily hot flashes (95% CI)	Improvement in severity, composite score,* or other measures†
Phyto-oestrogens				
Soy isoflavone extract[87]	Various components and doses	12 (4)	-1.45 (-2.82 to -0.03); 5 trials at 6 weeks; -0.97 (-1.82 to -0.12); 4 trials at 12-16 weeks; -1.22 (-2.02 to -0.42); 2 trials at 6 months	Improved in 4 of 9 trials
Dietary soy[88,89]	Soy beverage, powder, flour, protein, cereal, and nuttin	10 (1)	Improved in 1 of 7 trials	Improved in 2 of 10 trials
Red clover extract[90]	Promensil (40–160), ormotrill (57)	7 (none)	-0.44 (-1.49 to 0.58); 6 trials‡	Improved in 1 of 6 trials
Hop extract[91]	Hop-derived flavonoids	1 (none)	Not reported§	No difference
Flax[92]	Linseed (20–30)	2 (none)	No difference	No difference
Topical agents[93,94]	Phyto-oestrogen cream, wild yam cream	2 (none)	No difference	No difference
Black cohosh[95–98]	(40–160)	7 (2)	No difference	Improved in 3 of 7 trials
Dietary combinations[99,100]	Soy isoflavones and black cohosh; Actaplant, Vigrel and Blackcohosh	3 (none)	No difference	Improved in 2 of 3 trials
Chinese herbs[72]	Ginseng, ginkgo, dong quai, pueraria lobata, combinations	6 (none)	Not reported§	No difference
Other supplements[101–107]	Vitamin E, Eevy, phospholipid liposomes, evening primrose oil, botanical formulas, guaf gum, pollen extract, DHEA	8 (1)	No difference	Improved in 3 of 8 trials
Manual therapies[108]	Osteopathic manipulations	1 (none)	Not reported§	Improved hot flashes and night sweats
Energy therapies[109,110]	Reflexology, magnets	2 (1)	Improved with placebo as magnets	No difference
Behavioural interventions[111]	Aerobic exercise	1 (1)	No difference	Not reported§
Acupuncture[112,113]	Various treatments	3 (none)	No difference	No difference

DHEA=dehydroepiandosterone. *Frequency and severity. †Additional measures of hot flashes are included in this column because few trials of non-prescribed therapies provided severity and composite measures comparable to trials of standardised prescribed therapies. ‡Based on meta-analysis of trials. §Between-group differences not reported.

Table 3: Efficacy of non-prescribed therapies in placebo-controlled trials

placebo. A pilot study of acupuncture reduced night-time hot flashes,[112] but other trials of acupuncture did not show benefit.[183]

Therapies for non-vasomotor symptoms

Vaginal dryness and dyspareunia improved in trials of oral and vaginal forms of oestrogen.[123] For vaginal symptoms, the intravaginal oestradiol ring, oestradiol tablet, and conjugated equine oestrogen vaginal cream are similarly effective for relief of vaginal dryness, dyspareunia, resolution of atrophic signs, improvement in vaginal mucosal maturation indices, and reduction in vaginal pH.[123] Some women report reduced vaginal dryness with non-oestrogen moisturisers. Oestrogen does not improve urinary frequency and incontinence.[1] A few trials comparing oestrogen plus testosterone with oestrogen alone, or placebo, showed improved scores on sexual questionnaires addressing sexual interest and desire, responsiveness, and frequency of sexual activity, among other topics.[1] Tibolone could improve sexual interest and performance.[1]

Treatment of other symptoms, including sleep disturbances, mood changes, somatic complaints, and quality of life, have been assessed in trials for most therapies,[1] but results are inconclusive. This ambiguity might be due to the insensitivity and non-comparability of various measures and outcomes considered; the eventual resolution of symptoms as women progress through the menopausal transition; the placebo effect; or different effects in different groups of women (for instance, a positive effect only in women with the most severe symptoms, or comorbidities). Some symptoms could be secondary to others and improve as the primary symptom is treated, such as sleep disturbances arising from night sweats. As the epidemiological evidence indicates, some symptoms might not be related to menopause; if so, they would not be expected to improve with menopause-specific therapies such as oestrogen.

Conclusions

Menopause is an expected life event for midlife women. Most women have transient symptoms that are manageable with self-care approaches, such as wearing layers of clothing, and lowering stress. Some women ask health providers for help to manage menopausal symptoms, especially frequent and severe vasomotor symptoms and vaginal dryness, that interfere with healthy living. Coexistent health concerns can complicate the presentation, and require independent assessment. Social changes that are common in midlife, such as children leaving home, parents becoming ill or disabled, and the patient's changing role in society, can also affect the experience of menopause. Studies of menopause are vast in number, but incomplete in what they uncover.[124] Nonetheless, these results inform the recommendations of medical professional organisations,

and influence standards of practice.[125,126] Improved understanding of the menopausal transition, its symptoms, and therapies will permit a better response to the needs of patients.

Conflict of interest statement
I declare that I have no conflict of interest.

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Review

Understanding the pathophysiology of vasomotor symptoms (hot flushes and night sweats) that occur in perimenopause, menopause, and postmenopause life stages

D. C. Deecher[1], K. Dorries[2]

[1] Women's Health Research, Wyeth Pharmaceuticals, Collegeville, Pennsylvania, USA
[2] Advogent Group, Piscataway, New Jersey, USA

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Summary

Vasomotor symptoms (VMS), commonly called hot flashes or flushes (HFs) and night sweats, are the menopausal symptoms for which women seek treatment during menopause most often. VMS are a form of temperature dysfunction that occurs due to changes in gonadal hormones. Normally, core body temperature (CBT) remains within a specific range, oscillating with daily circadian rhythms. Physiological processes that conserve and dissipate heat are responsible for maintaining CBT, and tight regulation is important for maintenance of optimal internal organ function. Disruption of this tightly controlled temperature circuit results in exaggerated heat-loss responses and presents as VMS. The mechanistic role related to changes in gonadal hormones associated with VMS is not understood. Hormone therapy is the most effective treatment for VMS and other menopausal symptoms. Estrogens are known potent neuromodulators of numerous neuronal circuits throughout the central nervous system. Changing estrogen levels during menopause may impact multiple components involved in maintaining temperature homeostasis. Understanding the pathways and mechanisms involved in temperature regulation, probable causes of thermoregulatory dysfunction, and "brain adaptation" will guide drug discovery efforts. This review considers the processes and pathways involved in normal temperature regulation and the impact of fluctuating and declining hormones that result in VMS during the menopausal transition.

Keywords: Temperature; estrogen; woman

Introduction

At some time during the menopausal transition, as many as 80% of women will experience the classic menopausal vasomotor symptoms (VMS), hot flashes or flushes (HFs) and night sweats (National Institutes of Health 2005a). These symptoms can start to occur in the perimenopausal period (Soules et al. 2001), a stage of hormonal fluctuation that leads up to menopause (1 year after the last menstrual cycle), and can last throughout the postmenopausal phase (Rödström et al. 2002). Hot flushes and night sweats vary greatly in intensity, both between women and within individual women, over time. Mild HFs are experienced as a transient warming sensation, while severe symptoms may include sudden and intense heat spreading over the upper body and face, reddening of the skin or flushing, and severe perspiration. In one survey, more than half of the symptomatic women reported that flushing was followed by chills and shivering (Kronenberg 1990). Other symptoms associated with HF episodes include pressure in the head or chest, anxiety, nausea, and changes in heart rate and breathing. Night sweats are HFs that occur with heavy perspiration during sleep and cause sleep disruption (Woodward and Freedman 1994). Additionally, VMS may cause an increase in vulnerability in some women, to other physical (somatic) (Dugan et al. 2006; Kronenberg 1999) and psychological (mood disturbance) (Joffe et al. 2002) symptoms that result in a reduced quality of life and diminished work production (Utian 2005). Hot flush episodes generally last 1–5 min, although a small percentage of women report flushes

Correspondence: Darlene C. Deecher, PhD, Wyeth Research, 500 Arcola Road RN3164, Collegeville, PA 19426, USA
e-mail: deeched@wyeth.com

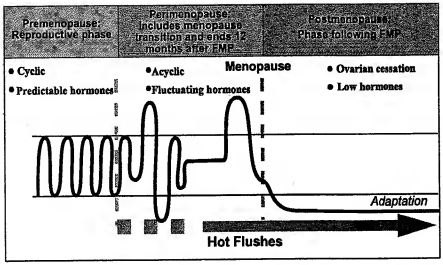

Fig. 1. Relationship between estrogen and a woman's reproductive phases and the occurrence of hot flushes. The reproductive phase is characterized by cyclic and predictable estrogen levels. During perimenopause, hormones fluctuate and become acyclic. During this period, many women experience VMS; although severe, the frequency is transient. During the postmenopausal period, women can experience severe and persistent VMS due to the declining levels of ovarian hormones. For most women, VMS eventually diminish over time. *FMP* final menstrual period

lasting up to 15 min (Kronenberg 1990). These VMS are associated with the fluctuating and eventual decline of ovarian hormone levels during and following the menopausal transition. They also occur in cancer survivors such as women with loss of ovarian function due to breast cancer treatment (Mom et al. 2006) and men who have undergone androgen ablation therapy (Holzbeierlein et al. 2003).

Changing estrogen levels play a role in the onset of VMS. Estrogen therapy has been shown to relieve VMS, reducing the number of HFs by as much as 95% in menopausal women (Baerug et al. 1998). In addition, many women who experience an abrupt onset of menopause brought on by oophorectomy have more severe symptoms than women who go through a natural, gradual transition (Hendrix 2005). Whether there is a direct relationship between circulating estrogen levels and the prevalence of HFs remains controversial (Øverlie et al. 2002; Randolph et al. 2005); the occurrence of VMS appears to be associated with the unpredictable fluctuations in estrogen levels occurring during the perimenopausal period as well as the diminished levels after menopause (Berendsen 2000; Freedman 2001; Deecher 2005) (Fig. 1). According to a study of 1400 women older than 25 years, women start reporting HFs as early as 38 years of age, while cycles are still predictable, suggesting that changes in ovarian function have started to occur (Rödström et al. 2002). These symptoms peak in late perimenopause or early menopause (average age, 52–54 years) and coincide with the final menstrual period (FMP) (Rödström et al. 2002; National Institutes of Health 2005a). For most women, HFs and night sweats eventually diminish in frequency and severity in the postmenopausal period (Guthrie et al. 2004; Avis et al. 2005) but for some women, VMS may last throughout the rest of their lifetime (Rödström et al. 2002).

VMS are believed to result from a dysfunction in the tightly controlled temperature circuitry leading to an exaggerated activation of heat dissipation responses, including peripheral vasodilation and sweating. Although in this review, the focus is on gonadal hormone-induced VMS, specific diseases, medications and neuronal damage can also cause thermoregulatory dysfunction. In brief, this important thermoregulatory circuitry is made up of 3 main components: the brain, the internal body cavity, and the peripheral vasculature (Deecher 2005). These components work together to maintain temperature homeostasis. In addition, other thermoregulatory zones provide temperature inputs. The body's various thermoregulatory zones send temperature signals to the corresponding thermoregulatory centers in the brain, particularly the hypothalamus. These centers use the signals to maintain optimal core body temperature (CBT) by inducing vasodilation to dissipate heat or vasoconstriction to conserve heat. Thus, an HF is a rapid, exaggerated response causing an intense heat sensation (flash), upper body skin reddening (flush), and increased skin blood flow resulting in changes in heart rate and blood pressure. It is hypothesized that the body is not really in a "hyperthermic" state, but that there is a miscommunication in temperature signaling that regulates normal temperature responses. Therefore, the message to rapidly reduce CBT results in extreme vasodilation followed by sweating and in some cases drenching

perspiration, especially at night, which can lead to sleep disruption (Kronenberg 1990; North American Menopause Society 2004a). Often, the extreme heat loss caused by the vasodilation of blood vessels results in chills and shivering as the body attempts to compensate for the loss (Freedman 2001).

Hormone therapy (HT) has long been the standard treatment for HFs and night sweats (North American Menopause Society 2004b); however, there is an unmet need for a safe and effective nonhormonal treatment for VMS to complement existing approved therapies (National Institutes of Health 2005b). In order to address this need, the underlying pathophysiology of VMS and the potential pathways, mechanisms, and targets involved in temperature regulation must be understood. This paper discusses normal thermoregulatory function and the impact of fluctuating and declining hormone levels that result in VMS during and following the menopausal transition.

Thermal homeostasis and regulation

Temperature homeostasis is a dynamic state of stability between an animal's internal and external environments. When functioning properly, the thermoregulatory system monitors and maintains CBT within a specific range required for optimal organ integrity and function regardless of environmental temperatures. When CBT falls below the optimal range required for maintenance of normal organ function, peripheral vasoconstriction and shivering are initiated to conserve body heat and raise internal temperature (Fig. 2). When it exceeds the optimal range, peripheral vasodilation and sweating are triggered and excess heat is dissipated through the skin by radiation and evaporative cooling processes (Charkoudian 2003). These 2 thresholds, the upper (sweating) threshold which triggers heat loss and the lower (shivering) threshold which triggers heat conservation or generation, define the thermoneutral zone (Cabanac and Massonnet 1977). The core temperature thermoneutral zone is maintained within defined (preset) limits that vary over the circadian cycle (Hensel 1973; Deecher 2005).

Temperature regulation is a complex, highly regulated, and integrated network of neuroendocrine, autonomic, and somatomotor responses (Deecher 2005). The temperature circuitry is a bidirectional feedback loop that communicates between 3 major communication centers. The 3 major components involved in thermoregulatory function (Fig. 3) consist of afferent thermosensitive pathways that provide information about CBT,

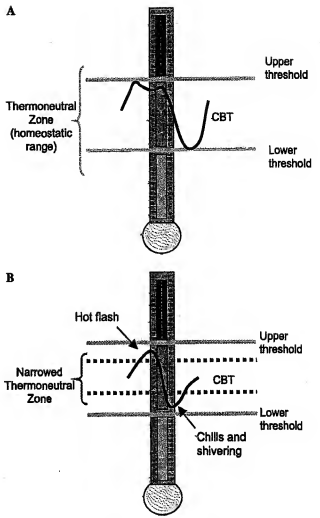

Fig. 2. Maintenance of core body temperature (CBT) is critical to organ integrity and optimal function (Deecher 2005). It has been hypothesized that core temperature is regulated between an upper threshold for sweating (heat dissipation) and a lower threshold for shivering (heat generation). Within the thermoneutral zone, major thermoregulatory responses such as sweating and shivering do not occur. These mechanisms maintain temperatures within the designated thresholds (Freedman 2005). A Normal temperature regulation. B Dysfunctional temperature regulation

central processing areas in the central nervous system (CNS), and peripheral vasculature, which receives efferent signals controlling thermoregulatory responses. Changes in CBT are communicated to the brain by heat- and cold-sensitive fibers in the CNS (Boulant 1998), deep body tissues, and skin (Boulant and Gonzalez 1977). Deep body temperature sensors are located in the gastrointestinal tract and other internal organs, intra-abdominal veins, and the spinal cord (Simon 2000; Romanovsky 2007). Thermosensitive nerve fibers from skin and deep tissues both contribute to generating thermoregulatory responses (Frank et al. 1999).

Integration of temperature information occurs at multiple levels in the CNS, but the hypothalamus, specifically the anterior hypothalamus/preoptic area (POA), is

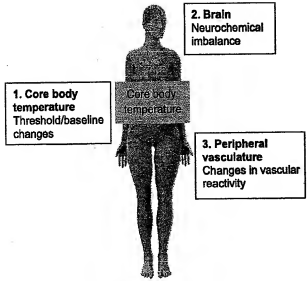

Fig. 3. The 3 major components involved in thermoregulatory function include afferent thermosensitive pathways providing information about core body temperature (CBT); central processing areas in the CNS; and peripheral vasculature, which receives efferent signals controlling vasodilation and vasoconstriction. Dysregulation at one or more of these sites can result in miscommunication and impaired temperature regulation. Figure reproduced from Deecher (2005) with modifications

considered to be the major CNS thermoregulatory processing center (Crawshaw et al. 1985; Romanovsky 2007). The POA projects to multiple effectors in the brainstem and spinal cord via the medial forebrain bundle (Boulant 2000). Warm-sensitive neurons in the POA appear to exert control over heat-loss effectors located in the lateral hypothalamus, periaqueductal grey matter, and reticular formation (Zhang et al. 1997), which are responsible for peripheral vasodilation and sweating (Bruck and Zeisberger 1990; Boulant 2000).

The primary mechanisms for regulating CBT are changes in blood flow through the skin and subcutaneous area and sweating. Peripheral vasculature receives sympathetic input controlling both vasodilation and vasoconstriction responses (Charkoudian 2003). Thus, when CBT rises above the required maintenance preset limits, peripheral vasodilation is triggered, resulting in increased blood flow to peripheral blood vessels. Conversely, when the temperature drops below the CBT preset limits, reduced blood flow in the peripheral blood vessels occurs as a means of retaining heat in the body (Charkoudian 2003). Chills and shivering may follow an HF or night sweat episode in order to regenerate excessive heat loss and reestablish normal CBT.

Multiple levels of thermoregulatory neural circuitry, central and peripheral, are under catecholinergic and/or serotonergic control. Serotonergic cells from the dorsal raphe nucleus (DRN) of the brainstem project to the POA, where mRNA for pre- and postsynaptic serotonin (5-HT) receptors have been localized in nonhuman primates (Gundlah et al. 1999; Bethea et al. 2002). The POA is also a target for norepinephrine (NE) pathways. The POA receives NE input from the nucleus of the solitary tract and the locus coeruleus. The existence of an α-adrenoceptor mRNA and β-adrenergic receptor activation have been demonstrated in the POA and hypothalamus (Petitti and Etgen 1990; Karkanias et al. 1996, 1997). Vasomotor effectors controlling peripheral vasodilation and vasoconstriction are also modulated by noradrenergic and serotonergic input (Martin 1994; Abdelmawla et al. 1999).

Thermoregulatory dysfunction

Thermoregulatory dysfunction appears to result from a disruption or miscommunication in the complex signaling and information processing between CBT, brain, and peripheral vasculature. Such disruptions might occur at one or more of these levels, and can have a variety of possible causes, including disease states, drug-induced effects, and gonadal hormone changes. Damage to CNS structures, particularly the hypothalamus, from injury or disease can disrupt temperature homeostasis. Significant changes in thresholds for thermoregulatory responses are associated with lesions to the hypothalamus in patients with multiple sclerosis (Sullivan et al. 1987; Edwards et al. 1996; White et al. 1996; Kurz et al. 1998) and traumatic brain injury, which when associated with damage to the hypothalamus (Crompton 1971), can result in posttraumatic hyperthermia (Thompson et al. 2003).

A commonly recognized example of thermoregulatory dysfunction is VMS associated with menopause. However, VMS are also reported by other patients that are not menopausal but, in some cases, are associated with changes in levels of circulating gonadal hormones or specific drug interactions with estrogen receptors (i.e., raloxifene, tamoxifen) (Land et al. 2006; Jordan 2007). For example, women with a history of breast cancer often experience VMS, as common chemotherapeutic agents may cause premature ovarian failure resulting in abrupt ovarian hormone level decline. In addition, these women may have been placed on an anti-estrogenic agent as a cancer preventative such as tamoxifen (Land et al. 2006) and aromatase inhibitors (Mom et al. 2006). Hot flushes are also experienced by men who receive androgen ablation or androgen deprivation therapy for prostate cancer, treatments that dramatically lower plasma testosterone levels, which, in

turn, lower available brain estrogen from aromatization (Holzbeierlein et al. 2003).

Thermoregulatory dysfunction associated with menopause

Years before the FMP, ovarian function begins to decline and estrogen levels fluctuate dramatically (Rödström et al. 2002; Bachmann 2005; Santoro 2005). In a review of studies documenting hormonal changes through the menopausal transition, Burger and colleagues (2002) concluded, "The most-noteworthy characteristic of the perimenopause stage is significant hormonal variability." Burger et al. (2002) cited several studies in which perimenopausal estradiol (a major endogenous human estrogen) levels or excretion patterns were characterized by large variations characteristic of abrupt increases or decreases. Santoro and colleagues (1996) showed that women in the menopausal transition had periods of anovulatory cycles and periods of time when urine estrogen metabolite (estrone) levels almost double the premenopausal stage concentrations. They also demonstrated that during this perimenopausal period, women may experience acyclic intervals with low, tonic estradiol levels characteristic of postmenopause. This unpredictable period of estrogen instability is thought to contribute (directly or indirectly) to a variety of menopausal complaints, including physical (VMS, sleep disturbances, urogenital complaints [Nelson et al. 2005]), psychological (irritability, depressive symptoms, mood disturbances, low libido [Dennerstein et al. 1994; Cohen et al. 2006; Freeman et al. 2006]), and somatic (aches and pains, fatigue [Shaver and Paulsen 1993]) symptoms.

The precise mechanisms underlying the pathophysiology of VMS are unknown, but there are at least 3 proposed hypotheses that have been studied. Various elements of these proposed hypotheses may contribute, in part, to this thermoregulatory dysfunction. The most prominent hypothesis, initially proposed by Tataryn et al. (1980), is that there is a change in the predefined acceptable temperature limits (thermoregulatory set points) or a miscommunication of these set points. A narrowing of this thermoneutral zone may occur, such that small, normally insignificant elevations in CBT signal a heat dissipation response, triggering an exaggerated reaction, i.e., hot flush (Freedman 2005) (Fig. 3). Freedman and his colleagues have carried out a series of experiments addressing this hypothesis (Freedman et al. 1995; Freedman and Woodward 1995, 1996; Freedman and Krell 1999; Freedman 2001). In these studies, they examined the relationship between CBT and the onset of heat-loss and heat-conserving responses. Core body temperature was measured in symptomatic and asymptomatic menopausal women using radiotelemetry pills. The subjects were warmed or cooled and thresholds for shivering and sweating were determined. The results of the experiments indicated that the shivering threshold is raised (Freedman and Krell 1995) and the sweating threshold is lowered (Freedman and Krell 1999), such that the normally acceptable temperature limit (thermoregulatory neutral zone) is significantly narrowed, from the normal 0.4 °C to "virtually nonexistent", in symptomatic menopausal women (Freedman and Krell 1996; Freedman 2001). Studies further indicated that HFs are, in most cases, preceded by small increases in CBT (Freedman et al. 1995; Freedman and Woodward 1996). Warming studies demonstrated that raising CBT slightly will trigger sweating and vasodilation in menopausal women with VMS but not asymptomatic menopausal women (Freedman 2001). Thus, in symptomatic menopausal women, small changes in CBT that would be tolerated under normal physiological circumstances now trigger anomalous heat dissipation responses (Freedman and Krell 1999), such as the extreme vasodilation and sweating reported by women with VMS associated with menopause.

A second hypothesis regarding the cause of VMS is related to the loss of responsiveness of the peripheral vasculature. Responses to thermal challenges in skin circulation are vital to normal thermoregulation, involving a feedback loop to and from the vasculature in order to respond to changes in internal body temperature (Charkoudian 2003).

It has been postulated that disturbances in local and reflex thermoregulatory control of skin circulation may contribute to thermoregulatory dysfunction. Changes in vascular reactivity may interfere with the ability of blood vessels to respond rapidly and to the appropriate degree, resulting in an exaggerated response (Charkoudian 2003). The occurrence of VMS may, in part, be due to a delay in the vasculature's response to messages arising at the level of the internal cavity sending signals that the temperature is too high and needs to be decreased. Estrogen and progesterone both appear to influence skin blood flow control (Brooks et al. 1997). The fluctuations in estradiol levels that occur during perimenopause may affect vascular reactivity responsiveness by altering the threshold for cutaneous vasodilation. The low levels of estradiol during the postmenopausal period may contribute to the reduced elasticity of the blood vessels, resulting in delayed responses due to

changes in internal body temperature (Joswig et al. 1999).

Another area of research that has been postulated to contribute to the pathophysiology of VMS is neurochemical alterations caused by changes in gonadal hormones during the menopausal transition period (Shanafelt et al. 2002). Numerous clinical trials assessing the efficacy of various centrally acting compounds have been conducted (Nelson et al. 2006a). Anticholinergic drugs have been experimentally tested based on the notion that the cholinergic system was involved in the dysfunction (Clayden 1972; Williams 1973; Clayden et al. 1974). Other agents such as clonidine (an alpha-2 adrenergic agonist) and gabapentin have been used with some success (North American Menopause Society 2004a; Deecher 2005; Nelson et al. 2006a). Additionally, the selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have also shown some effect in reducing VMS (Nelson et al. 2006b). These drugs are proposed to work by "restoring" altered levels of 5-HT and/or NE that are believed to be affected due to the loss of modulation by estrogens (Deecher et al. 2007). The efficacy of these compounds provides some support to the hypothesis that neurochemical imbalances in the brain may be an underlying cause of the thermoregulatory dysfunction that results in VMS associated with gonadal hormone changes.

Estrogens as neuromodulators

Estrogens are potent neuromodulators known to regulate the structure and function of numerous neuronal circuits throughout the CNS (Gould et al. 1990; Woolley and McEwen 1993; McEwen and Alves 1999; McEwen 2001; Genazzani et al. 2007). Over the course of the human life span, the female brain must respond and adapt to changes in estradiol levels dependent on her life stage. Although puberty requires that both male and female brains adapt to a new hormonal environment, the cyclic and transient hormonal fluctuations of the female menstrual cycle may require a very different capacity of flexibility and functional responsiveness. During the reproductive years, the female brain must develop flexible and responsive mechanisms due to cyclic and synchronized changes in neuroendocrine input in order to maintain precisely timed ovulatory events. During the menopausal transition, these timed cycles become asynchronized and unpredictable resulting in ovarian hormone levels being exaggerated (Santoro et al. 1996) (Fig. 1), demanding even greater flexibility in neuronal responsiveness (Gibbs 1998; McEwen 2001). This period of the life cycle could be considered a time of unpredictable hormonal messaging. Thus, the brain and the neurochemical mechanisms responsible for maintaining homeostasis are unable to adjust rapidly or efficiently to optimally function. It is hypothesized that after menopause, the female brain must adapt to the absence of cyclic levels of ovarian hormones and establish a new baseline of homeostasis in order to maintain normal brain function (Birge 2003). The inability to respond or establish a new baseline of neuronal function could lead to increased susceptibility to brain-related dysfunctions including thermoregulatory dysfunctions.

Therefore, unexpected changes in estrogen levels during the menopausal transition may impact multiple components involved in maintaining temperature homeostasis. Estrogens have been shown to control gene expression, up- or downregulating numerous components of cell signaling pathways, including membrane receptor proteins, transporters, and enzymes involved in synthesis or degradation of neurotransmitters, as well as directly altering neuron membrane currents and firing patterns (McEwen and Alves 1999; Bethea et al. 2000a; McEwen 2002). Unpredictable fluctuations and the decline of gonadal hormones are believed to affect neural systems regulated by estrogens. The hypothalamus will be particularly affected by these changes in gonadal hormones since it is highly hormone-responsive due to the expression of both estrogen and progesterone receptors (Gould et al. 1990; Woolley and McEwen 1993; McEwen 2001; McEwen and Alves 1999). This region of the brain is also considered a key site for integration of thermal information and control of thermoregulatory responses (Boulant 2000). Decreasing hormone levels may lead to diminished neuronal function resulting in a change in the balance of key neurotransmitters involved in temperature regulation such as 5-HT and NE.

Estrogens may modulate any level of the thermoregulatory pathway. However, there is a wealth of evidence that the hypothalamus, and specifically the POA, is hormone responsive, and that estrogen may regulate the functional activity of neurotransmitter systems within the POA. Estrogen receptors have been localized in regions associated with the thermoregulatory system (Bethea et al. 1996; Gundlah et al. 2000; Osterlund et al. 2000), indicating that those areas may be responsive to estrogen and that their structure or function may be influenced by changes in estrogen levels, as during

the menopausal transition. There is supporting in vitro and in vivo preclinical evidence that estrogens are neuromodulators of the serotonergic and noradrenergic systems that are believed to play a role in the maintenance of temperature regulation in the brain as well as the periphery. Various animal reports have shown that estrogen receptors are expressed in both NE and 5-HT projections to the hypothalamus (Kalló et al. 1992; Bethea et al. 2000a; Lu et al. 2001; Temel et al. 2002), and that estrogens can regulate both serotonergic and noradrenergic systems by modulating production, release, recycling/elimination, and receptor activity (Shanafelt et al. 2002; Bachmann 2005).

The effects of fluctuating estrogen levels on NE and 5-HT have been examined specifically with respect to thermoregulatory function in animal models (Maswood et al. 2006; Deecher et al. 2007), and modulation of these neurotransmitter systems in the POA have been studied in the context of other functions as well. Estrogens have been reported to influence 5-HT and NE synthesis, density of pre- and postsynaptic binding sites, and deactivation via neurotransmitter reuptake and degradation (Genazzani et al. 1997; Bethea et al. 1998, 2002; McEwen and Alves 1999; Herbison et al. 2000; Etgen et al. 2001; Amin et al. 2005). Estrogens appear to increase the availability of 5-HT by boosting the capacity to synthesize the transmitter and by slowing its degradation (Pecins-Thompson et al. 1996; Bethea et al. 2000b; Gundlah et al. 2002, 2005; Hiroi et al. 2005; Sanchez et al. 2005). It also regulates 5-HT receptor density and binding and slows the transmitter's removal from the synapse (Lu and Bethea 2002; Le Saux and Di Paolo 2005). Using both in vitro and in vivo techniques, estrogens have been shown to modulate the noradrenergic system in ways similar to those demonstrated for 5-HT, with affects on synthesis (Serova et al. 2002, 2004) and degradation (Gundlah et al. 2002), as well as downstream receptor signaling and function (Karkanias and Etgen 1994).

Such estrogen-associated modulations of NE and 5-HT signaling have been proposed to be one means by which thermoregulatory dysfunction occurs due to hormonal changes (Deecher et al. 2007). Thus, fluctuations in estrogen levels during the menopausal transition are hypothesized to disrupt the normal balance of NE and 5-HT maintained under cyclic estrogen control, thereby altering downstream signaling in thermoregulatory circuits as well as other neurologically important pathways. Clinical trial results also support the hypothesis that 5-HT and NE may play an important role in thermoregulation showing that SSRIs or SNRIs can alleviate VMS, reducing HF scores by up to 65% (Loprinzi et al. 2000, 2002; Stearns et al. 2003, 2005), although it should be noted, new clinical reporting is suggesting that increasing 5-HT alone may not be adequate to alleviate VMS (Suvanto-Luukkonen et al. 2005; Grady et al. 2007). Moreover, research shows that plasma NE levels are elevated before and during HFs, and that production and release of NE in the hypothalamus is inhibited by metabolic by-products of estrogen (Freedman and Krell 1999; Shanafelt et al. 2002).

Taken together, in vitro and in vivo preclinical data with clinical findings support the hypothesis that changes in estrogen levels impact important neurochemical processes involved in temperature regulation.

Adaptation to gonadal hormone changes

As mentioned earlier, VMS have their onset in the early perimenopausal period (Rödström et al. 2002). During the perimenopausal period, the occurrence of VMS is transient yet severe, due to the irregularity and unpredictability of hormone levels (Burger 1996). These symptoms diminish over time in the postmenopausal period, although some women report these symptoms long after the last menstrual cycle (Rödström et al. 2002). The slow progression of the reduction and eventual disappearance of VMS suggests that over time the brain must "reset" or "adapt" to a different neurochemical level in order to restore normal temperature regulation. It appears this adaptation period is individually determined and can require a rather extended amount of time to readapt brain function, reset temperature thresholds, and return to normal temperature responses. Evidence suggests that estradiol is the primary gonadal hormone responsible for VMS and when given to women, estrogens have been shown to alleviate these symptoms. For the majority of women taking HT to treat menopausal VMS, the symptoms recur after cessation of HT, suggesting that VMS are relieved but not eliminated (Haimov-Kochman et al. 2006; Ness et al. 2006). This suggests that there is a period of time during which brain function must reset and adjust to the "hypoestrogenic" state after menopause and this process is referred to as "brain adaptation". The idea of "brain adaptation" supports the hypothesis that changes in neurochemical processes are involved in thermoregulatory dysfunction. Most women adapt to this new "hypoestrogenic" state, although there are individual differences in the degree and duration of suffering before adaptation is complete. It should be noted that some women will experience

VMS throughout their remaining life span (Rödström et al. 2002).

Conclusions

Thermoregulatory dysfunction appears to result from a miscommunication in the complex signaling and information processing between the CBT, brain, and vascular system. VMS, commonly referred to as hot flashes or flushes and night sweats, are extreme thermoregulatory responses resulting from a disruption in the ability to keep body temperature within a specific optimal range. The incidence of VMS has been reported by up to 80% of all women advancing through menopause, with symptoms diminishing over time in the postmenopausal period. The slow progressive lessening and eventual disappearance of VMS suggest that over time the brain must "reset" or "adapt" to different neurochemical levels in order to restore normal temperature regulation. This period of "brain adaptation" may be a key element to study in order to further understand the pathophysiology of thermoregulatory dysfunction and develop effective nonhormonal therapies for VMS associated with menopause.

A direct relationship between plasma estradiol levels and the occurrence of VMS has not been unequivocally demonstrated (Øverlie et al. 2002; Randolph et al. 2005), but the dramatic fluctuations in hormone levels during the perimenopausal transition and the declining levels of estradiol overall in postmenopause are thought to disrupt central thermoregulatory processing, perhaps via interactions with the neurotransmitter systems important to temperature control. The POA of the hypothalamus, believed to be the main central processing area for temperature regulation, is also a site of estrogen sensitivity. The NE and 5-HT signaling pathways in the POA, both critical to thermoregulatory processing, are thought to be affected by estrogen changes. It is hypothesized that fluctuating and declining hormone levels modulate key neurotransmitters and the expression or function of their receptors, thereby altering the response patterns of the thermoregulatory circuits and changing the thresholds for sweating and shivering responses. This hypothesis predicts that agents that stabilize NE and 5-HT could alleviate VMS, and in several clinical trials 5-HT and NE modulators have been shown to be effective. It is important to note that there is reciprocal feedback between noradrenergic and serotonergic neurons, with each system ultimately influencing the activity of both neurotransmitters (Guyton and Hall 2006). Recent negative results from a placebo-controlled trial of the SSRIs citalopram and fluoxetine (Suvanto-Luukkonen et al. 2005) suggest modulation of 5-HT alone is not sufficient to alleviate VMS, and agents that contain both 5-HT and NE activity (i.e., SNRIs) may be necessary for effective therapy (Loprinzi et al. 2000).

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